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(72)Inventor : JINNO SHUJI
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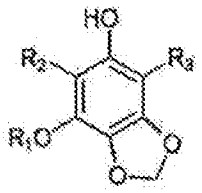
(54) NOVEL BENZODIOXOL DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide the subject novel benzodioxol derivative that has the effect of inhibiting peroxide lipids and is useful as a medicine, cosmetic and chemical or the like.
SOLUTION: This compound is represented by the formula [R1 is H, a lower alkyl; at least one of R2 and R3 is an aromatic ring, a hetero ring (the benzofuran ring is removed) and the remaining is H], typically 5-phenyl-6-hydroxy-4-methoxy-1,3-benzodioxol. The compound of the formula, in the case of the typical compound, is prepared by halogenating 4-methoxy-6-hydroxy-1,3- benzodioxol to form 5-bromo-4-methoxy-6-hydroxy-1,3-benzodioxol, protecting the hydroxyl group, then followed by deprotection. This compound is useful as a therapeutic agent for cancers, arteriosclerosis, Parkinson's disease or the like.



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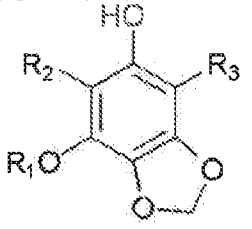
4C086 AA02 AA03 BA13 BB02 GA02 GA03 NA14 ZC33

(54)【発明の名称】　新規ベンゾジオキソール誘導体

(57)【要約】
【課題】　本発明は、ベンゾジオキソール誘導体が生理作用を有する点に着目し、有機合成によりその中間体およびそれら誘導体を合成し、得られた化合物の性質を探索し、高い抗酸化作用を有する新規誘導体を提供することを課題とする。
【解決手段】　本発明は、一般式（１）



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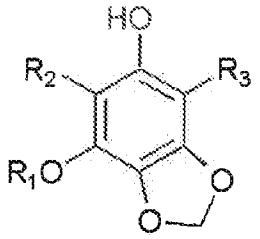
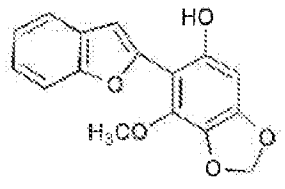
（ここで、Ｒ１は水素あるいは低級アルキル基であり、Ｒ２およびＲ３の少なくとも一方は、芳香環あるいはヘテロ環（ベンゾフラン環を除く）であり、残りは水素から選択される任意の置換基）で表されるベンゾジオキソール誘導体およびその塩。

【特許請求の範囲】
【請求項１】一般式（１）
【化１】



(1)

〔ここで、Ｒ１は水素あるいは低級アルキル基であり、Ｒ２およびＲ３の少なくとも一方は、芳香環あるいはヘテロ環（ベンゾフラン環を除く）であり、残りは水素から選択される任意の置換基〕で表されるベンゾジオキソール誘導体およびその塩。
【請求項２】　一般式（１）中、少なくともＲ２が芳香環あるいはヘテロ環（ベンゾフラン環を除く）である請求項１のベンゾジオキソール誘導体。
【発明の詳細な説明】
【０００１】
【産業の属する技術分野】本発明は、新規ベンゾジオキソール誘導体に関する。さらに詳しくは、この発明は、抗酸化作用や医療品等に有用な過酸化脂質抑制作用を有する新規ベンゾジオキソール誘導体に関する。
【０００２】
【従来の技術】近年、ガン、動脈硬化症、パーキンソン病、糖尿病、炎症、さらには老化等の現象と生体内酸化反応との関連性が指摘されており、生体内の酸化機構を制御することのできる薬剤として抗酸化物質への期待が高まっている。
【０００３】
【発明が解決しようとする課題】本発明は過酸化脂質抑制効果を有するベンゾジオキソール誘導体を提供することを目的とする。酵母より赤血球の溶血を防ぐ物質として、次の式（２）で示される化合物１が見いだされているが（J.Am.Chem. Soc., 80, 385-389, 1958）、ベンゾジオキソール誘導体の過酸化脂質抑制効果については報告例はない。
【０００４】
【化２】



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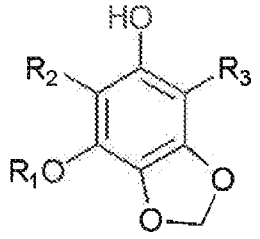
【０００５】
【課題を解決するための手段】本発明は、ベンゾジオキソール誘導体に過酸化脂質抑制効果を見いだし、有機合成によりその中間体およびそれら誘導体を合成し、得られた化合物の性質を探索し、高い抗酸化作用（過酸化脂質抑制作用）を有する新規誘導体を提供するものである。本発明は、一般式（１）
【０００６】
【化３】



(1)

〔ここで、Ｒ１は水素あるいは低級アルキル基であり、Ｒ２およびＲ３の少なくとも一方は、芳香環あるいはヘテロ環（ベンゾフラン環を除く）であり残りは水素から選択される任意の置換基〕で表されるベンゾジオキソール誘導体およびその塩を提供する。
【０００７】
【発明の実施の形態】以下に本発明について詳細に説明する。本発明において、「低級アルキル基」とは、炭素数８個までの直鎖状、分枝鎖状または環状を意味する。本発明において、「芳香環あるいはヘテロ環」とは、有機化学上許容される官能基を意味し、それらは例えば、フェニル基、ナフタレン基、チオフェン基、フラン基、ピリジン基、ベンゾチオフェン基等およびそれらの置換基体である。また、本発明化合物の塩とは、製薬学上許容される塩を意味し、それらは例えば、ナトリウム塩、カリウム塩、カルシウム塩、アンモニウム塩、アルミニウム塩である。本発明のベンゾジオキソール誘導体は新規物質であり、過酸化脂質抑制作用を有し、医薬品、化粧品、化成品等に使用される化学物質として有用である。その製造方法は、パラジウム触媒存在下、ハロゲン化ベンゾジオキソール体と有機ボロン酸あるいは有機スズ試薬を用いた炭素－炭素結合を鍵反応とする合成法を用いることにより得られる。その製造の詳細は実施例で説明する。
【０００８】また、本発明でベンゾジオキソール誘導体には過酸化脂質抑制作用があることが確認でされ、本発明の新規ベンゾジオキソール誘導体は、優れた過酸化脂質抑制作用を有することも確認されている。従って本発明の新規ベンゾジオキソール誘導体は、生体内過酸化反応が関与していると考えられる諸疾患、例えば、ガン、動脈硬化症、パーキンソン病、糖尿病、炎症の治療薬として有用である。この目的のためには、本発明の化合物を慣用的な製剤技術に従って製造される各種の剤型、例えば、散剤、顆粒剤、錠剤、糖衣剤、アンプル剤、カプセル剤等の経口投与剤、皮下、筋肉内もしくは静脈内投与剤、座剤等とすることができる。上記製剤化には、通常の増量剤、結合剤、崩壊剤、ｐＨ調節剤、溶解剤などの添加剤を用いることができる。

【０００９】本発明の新規ベンゾジオキソール誘導体の治療患者に対する投与量は、患者の年齢、疾病の種類および状態などにより変動しうるが、通常成人に対して一日当たり１０～５０００ｍｇを１～数回に分けて投与することができる。

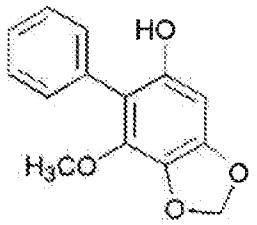
【００１０】

【実施例】本発明を実施例によって説明する。実施例は実施の一態様であり、本発明を限定するものではない。

【００１１】（実施例１）5-フェニル-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物２）の合成

【００１２】

【化４】



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【００１３】工程１　5-ブロモ-4-メトキシ-6-ヒドロキシ-1,3-ベンゾジオキソールの合成

4-メトキシ-6-ヒドロキシ-1,3-ベンゾジオキソール(2.78g,16.5 mmol)を酢酸(13.9 mL)およびジクロルメタン(5.58 mL)に溶解し０℃で撹拌した。そこに臭素(0.864mL,16.3 mmol)を含むジクロルメタン(5.58 mL)溶液を滴下した。室温で１時間撹拌後、反応合物を氷水にあけ酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲルカラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=4：1）にて精製した。イソプロピルエーテルで再結晶し、標記化合物の結晶3.4g(83%)を得た。融点77.3-78.7℃。1H NMR (DMSO-d6, 400 MHz) δ 4.07(3H,s, CH3), 6.0 (2H, m, CH2), 6.46 (1H, s, Ar-H),8.26(1H, s, OH)。

【００１４】工程２　6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソールの合成

工程１で得られた5-ブロモ-4-メトキシ-6-ヒドロキシ-1,3-ベンゾジオキソール(2.55g,10.32 mmol)をジメチルホルムアミド5 mLに溶解し、水素化ナトリウム(416mg,10.4 mmol)を含むジメチルホルムアミド(2.5 mL)懸濁液に０℃で撹拌下、滴下した。室温で30分間撹拌後、ベンジルブロミド(1.25ml,10.5 mmol)を加えさらに室温で30分間撹拌した。反応混合物を氷水にあけ酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=4：1）にて精製し、標記化合物を油状物として2.78 g (80%)得た。1HNMR(CDCl3,400MHz) δ 4.07 (3H, s, CH3), 5.06 (2H, s, CH2), 5.90(2H, s, CH2), 6.34 (1H, s, Ar-H), 7.3-7.5(6H, m,Ar-H)。

【００１５】工程３　5-フェニル-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成

工程２で得られた6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール(300mg,0.89 mmol)、フェニルホウ酸(119mg, 0.98 mmol)、テトラブチルアンモニウムブロマイド(287mg, 0.89 mmol)、酢酸パラジウム(4mg, 0.018 mmol)、炭酸カリウム(307mg, 2.22 mmol)に水2mLを加え、90℃で1時間撹拌した。反応混合物を1N塩酸にあけ、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=20：1）にて精製した。標記化合物を油状物として241mg(81%)得た。1HNMR(CDCl3,400MHz) δ3.81(3H, s,CH3), 4.85 (2H, s, CH2), 5.92(2H, s,CH2),6.38 (1H, s, Ar-H), 7.1-7.4(10H,m, Ar-H)。MS(EI) m/z 334(M+, 100%), 243, 213, 91。

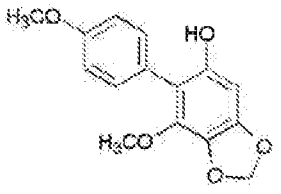
【００１６】工程４　5-フェニル-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成

工程３で得られた5-フェニル-6-ベンジロキシ-4-メトキシ-1,3-ベンゾジオキソール(200mg)を酢酸エチル(10mL)に溶解し、10%Pd-C(20mg)を加え室温で一晩撹拌し水素添加した。反応混合物をろ過し濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=5：1）にて精製し、石油エーテルで再結晶し、標記化合物の結晶136mg(93%)を得た。融点88.1-89.4℃。1HNMR(CDCl3,400MHz) δ3.83(3H, s, CH3), 4.78 (1H, brs, OH), 5.91 (2H,s, CH2),6.31 (1H, s, Ar-H), 7.32-7.34 (2H, m, Ar-H),7.37-7.41(1H, m, Ar-H), 7.46-7.50 (2H, m, Ar-H)。MS(EI)m/z 244 (M+, 100%), 199, 171, 115。

【００１７】（実施例２）　5-(4-メトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物３）の合成

【００１８】

【化５】



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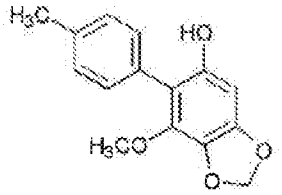
【００１９】実施例１のフェニルホウ酸の代わりに4-メトキシフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。融点83.0-83.8℃。1HNMR(CDCl3,400MHz) δ3.83(3H, s, CH3), 3.85 (3H, s, CH3), 4.79 (1H,brs, OH),5.90 (2H,s, CH2), 6.30 (1H, s, Ar-H),7.00-7.02(2H, m, Ar-H), 7.23-7.25 (2H, m, Ar-H)。MS(EI)m/z 274 (M+, 100%), 259, 229, 201, 145。

【００２０】（実施例３）　5-(4-メチルフェニル)-6-

ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物４）の合成

【００２１】

【化６】



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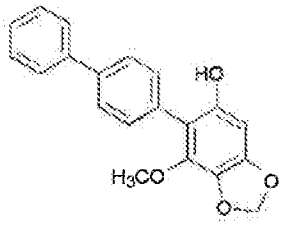
【００２２】実施例１のフェニルホウ酸の代わりに4-メチルフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。融点124.8-126.6℃。1HNMR(CDCl3,400MHz) δ2.40(3H, s, CH3), 3.83 (3H, s, CH3), 4.80 (1H,brs, OH),5.90 (2H,s, CH2), 6.30 (1H, s, Ar-H),7.20-7.22(2H, m, Ar-H), 7.28-7.30 (2H, m, Ar-H)。MS(EI)m/z 258 (M+, 100%), 243, 213, 185, 129。

【００２３】（実施例４）　5-(4-ビフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物５）の合成

【００２４】

【化７】



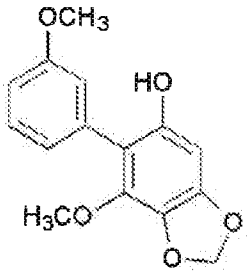
(6)

【００２５】実施例１のフェニルホウ酸の代わりに4-ビフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。融点141.8-143.5℃。1HNMR(CDCl3,400MHz) δ3.87(3H, s, CH3), 4.86 (1H, brs, OH), 5.91 (2H,s, CH2),6.33 (1H, s, Ar-H), 7.35-7.41 (3H, m, Ar-H),7.44-7.48(2H, m, Ar-H), 7.63-7.65 (2H, m, Ar-H),7.68-7.71(2H, m, Ar-H)。MS(EI)m/z 320 (M+, 100%), 275, 247, 191。

【００２６】（実施例５）　5-(3-メトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物６）の合成

【００２７】

【化８】



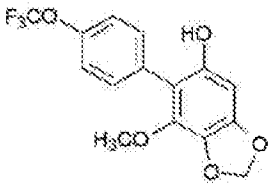
(7)

【００２８】実施例１のフェニルホウ酸の代わりに3-メトキシフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。1HNMR(CDCl3,400MHz) δ 3.83 (3H, s, CH3), 3.84 (3H, s, CH3),4.86(1H, brs, OH), 5.91 (2H, s, CH2), 6.31 (1H,s, Ar-H),6.86-6.95 (4H, m, Ar-H), 7.40 (1H, dd,J = 7.9, 7.9 Hz Ar-H)。

【００２９】（実施例６）　5-(4-トリフルオロメチルフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物７）の合成

【００３０】

【化９】



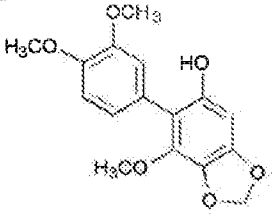
(8)

【００３１】実施例１のフェニルホウ酸の代わりに4-トリフルオロメチルフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。1HNMR(CDCl3,400MHz) δ 3.85 (3H, s, CH3), 4.62 (1H, brs, OH),5.91(2H, s, CH2), 6.30 (1H, s, Ar-H), 7.30-7.37(4H,m, Ar-H)。

【００３２】（実施例７）　5-(3,4-ジメトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物８）の合成

【００３３】

【化１０】



(9)

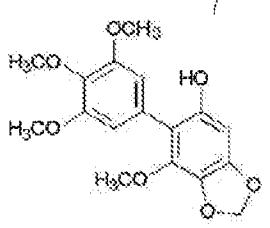
【００３４】実施例１のフェニルホウ酸の代わりに3,4-ジメトキシフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。1HNMR(CDCl3,400MHz) δ 3.85(3H, s, CH3), 3.88 (3H, s, CH3),3.93(3H, s, CH3), 4.88 (1H, brs, OH), 5.90 (2H,s, CH2),6.31 (1H, s, Ar-H), 6.83 (1H, d, J = 1.9Hz Ar-H),6.88 (1H, dd, J = 1.9, 8.0 Hz Ar-H), 6.98(1H, d, J = 8.0Hz Ar-H)。

【００３５】（実施例８）　5-(3,4,5-トリメトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物９）の合成

【００３６】

【化１１】

7



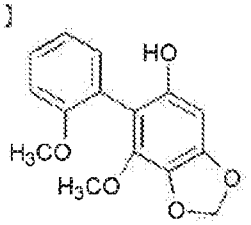
(10)

【００３７】実施例１のフェニルホウ酸の代わりに3,4,5-トリメトキシフェニルホウ酸を用いる以外は実施例１と同様にして標記化合物を得た。1HNMR（CDCl3,400MHz）δ3.86（6H，s，CH3），3.88（3H，s，CH3），3.90(3H，s，CH3），4.94（1H，brs，OH），5.91（2H,s，CH2），6.31（1H，s，Ar-H），6.53（2H，s，Ar-H）。

【００３８】（実施例９）　5-(2-メトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物１０）の合成

【００３９】

【化１２】



(11)

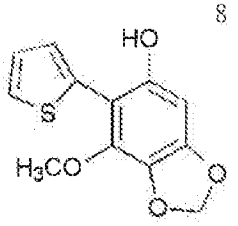
【００４０】実施例１で得られた6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール(360mg,1.07 mmol)、2-メトキシフェニルホウ酸（240 mg，1.61 mmol)、テトラキス（トリフェニルホスフィン）パラジウム(120mg,0.11 mmol)に2M 炭酸カリウム溶液（0.6 ml)、トルエン6 mLを加え、120℃で16時間撹拌した。反応混合物を1N塩酸にあけ、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=5：1）にて精製した。得られた油状物を酢酸エチル(10 mL)に溶解し、10%Pd-C(150mg)を加え室温で一晩撹拌し水素添加した。反応混合物をろ過し濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=3：1）にて精製し、標記化合物の結晶118 mg（40%)を得た。1H NMR(CDCl3,400MHz) δ 3.82（3H，s，CH3），3.83（3H，s，CH3），5.03(1H，brs，OH），5.91（2H，m，CH2），6.33（1H,s，Ar-H),7.03-7.06（2H，m，Ar-H），7.22-7.25（1H,m，Ar-H),7.37-7.41（1H，m，Ar-H)。

【００４１】（実施例１０）　5-(チエニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物１１）の合成

【００４２】

【化１３】

8



(12)

【００４３】工程１　5-(チエニル)-6-ベンジロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成

実施例１で得られた6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール(300mg,0.89 mmol)、2-(トリブチルスタニル)-チオフェン(565mL,1.78 mmol)、テトラキス（トリフェニルホスフィン）パラジウム(51mg,0.04 mmol)にHMPA5mLを加え、100℃で4時間撹拌した。反応混合物を1N塩酸にあけ、ジエチルエーテルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=5：1）にて精製した。標記化合物を油状物として281 mg(93%)を得た。1HNMR(CDCl3,400MHz) δ3.90(3H，s，CH3），4.96（2H，s，CH2），5.92(2H，s,CH2),6.38（1H，s，Ar-H），7.06-7.07（1H，m，Ar-H),7.27-7.34(7H,m，Ar-H)。MS(EI) m/z 340（M+），249（100%），219，91。

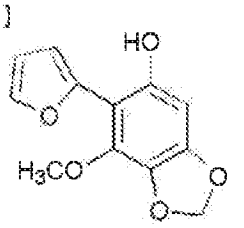
【００４４】工程２　5-(チエニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成

工程１で得られた5-(チエニル)-6-ベンジロキシ-4-メトキシ-1,3-ベンゾジオキソール(280mg)を酢酸エチル(10mL)に溶解し、10%Pd-C(150mg)を加え室温で一晩撹拌し水素添加した。反応混合物をろ過し濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：酢酸エチル=5：1）にて精製し、石油エーテルで再結晶し、標記化合物の結晶15mg(7%)を得た。融点75.6-77.0℃。1HNMR(CDCl3,400MHz) δ3.91(3H，s，CH3），5.21（1H，brs，OH），5.91（2H,s，CH2),6.31（1H，s，Ar-H），7.06（1H，dd，J= 0.8,3.5 Hz，Ar-H),7.15（1H,dd，J= 3.5，5.0 Hz，Ar-H),7.48（1H，dd，J= 0.8，5.0 Hz，Ar-H)。MS(EI)m/z250（M+，100%），235，219，205，121。

【００４５】（実施例１１）　5-(2-フラン)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物１２）の合成

【００４６】

【化１４】



(13)

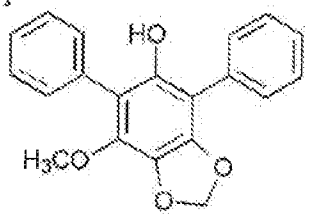
【００４７】実施例１０の6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール、2-(トリブチルスタ

ニル)-チオフェンの代わりに6-ブチルジメチルシリロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール、2-(トリブチルスタニル)-フランを用いる以外は実施例１０と同様にして得られた油状物をTHFに溶解しTBAFを加え脱保護し、標記化合物を得た。1HNMR(CDCl3,400MHz) δ 4.00 (3H, s, CH3), 7.4 (1H, brs, OH),5.90(2H, s, CH2), 6.29 (1H, s, Ar-H), 6.53-6.54(1H,m, Ar-H), 6.73-6.74 (1H, m, Ar-H), 7.48-7.49(1H,m, Ar-H)。

【００４８】（実施例１２）1,5-ジフェニル-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物１３）の合成

【００４９】

【化１５】



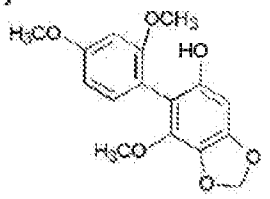
(14)

実施例１の5-フェニル-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの代わりに6-ベンジロキシ-1,5-ジブロモ-4-メトキシ-1,3-ベンゾジオキソールを用いる以外は実施例１と同様にして標記化合物を得た。1HNMR(CDCl3,400MHz) δ3.86 (3H, s, CH3), 4.93 (1H, brs, OH),5.93(2H, s, CH2), 7.37-7.59 (10H,m, Ar-H)。

【００５０】（実施例１３）　5-(2,4-ジメトキシフェニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソール（化合物１４）の合成

【００５１】

【化１６】



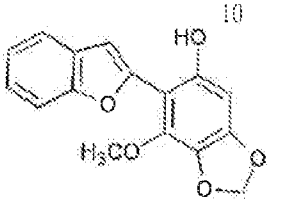
(15)

【００５２】実施例９の2-メトキシフェニルホウ酸の代わりに2,4-ジメトキシフェニルホウ酸を用いる以外は実施例９と同様にして標記化合物を得た。1HNMR(CDCl3,400MHz) δ 3.80 (3H, s, CH3), 3.81 (3H, s, CH3),3.85 (3H, s, CH3), 4.96 (1H, brs, OH), 5.90 (2H,m, CH2),6.32 (1H, s, Ar-H), 6.60-6.62 (2H, m, Ar-H),7.12-7.14(1H, m, Ar-H)。

【００５３】（参考例）5-(2-ベンゾフラニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成（化合物１）

【００５４】

【化１７】



(2)

【００５５】工程１　5-(2-ベンゾフラニル)-6-ベンジロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成
実施例１で得られた6-ベンジロキシ-5-ブロモ-4-メトキシ-1,3-ベンゾジオキソール(960mg, 2.82 mmol)、ベンゾフラン-2-ホウ酸(684mg,4.22 mmol)、トリス（o-トルイル）ホスフィン(128mg,0.421 mmol)、トリスベンジリデンアセトン二パラジウム・クロロホルム錯体(109mg, 0.105 mmol)、ジイソプロピルエチルアミン(0.982g,5.64 mmol)をジメチルホルムアミド10mLに溶解し、90℃で1時間撹拌した。反応混合物を水水にあけ、酢酸エチルで抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥、濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒；ヘキサン：ベンゼン=1：1）にて精製した。標記化合物を油状物として1.14g(100%)得た。1HNMR(CDCl3,400MHz) δ3.95(3H, s, CH3), 5.01 (2H, s, CH2), 5.95(2H, s,CH2),6.39 (1H, s, Ar-H), 6.83 (1H, s, Ar-H),6.8-7.6(10H,m, Ar-H)。MS(EI)m/z 374, 283, 255。

【００５６】工程２　5-(2-ベンゾフラニル)-6-ヒドロキシ-4-メトキシ-1,3-ベンゾジオキソールの合成
工程１で得られた5-(2-ベンゾフラニル)-6-ベンジロキシ-4-メトキシ-1,3-ベンゾジオキソール(1.14g,3.04 mmol)、を酢酸エチル(70mL)に溶解し，10%Pd-C(56mg)を加え室温で一晩撹拌し水素添加した。反応混合物をろ過し濃縮した。残渣をシリカゲル・カラムクロマトグラフィー（展開溶媒：酢酸エチル：ヘキサン=15：85）にて精製した。石油エーテルで再結晶し、標記化合物715mg(88%)を得た。融点118℃。1HNMR(Acetone-d6, 400 MHz) δ3.95(3H, s, CH3), 5.06 (2H, s,CH2), 5.93 (2H,s, CH2),6.31 (1H, s, Ar-H), 6.93 (1H, s, Ar-H),7.2-7.6(6H,m, Ar-H), 8.33 (1H, s, OH)。MS(EI)m/z 284, 269, 142。

【００５７】（抗酸化活性測定試験）過酸化脂質抑制試験はBiochem.Biophys.Res. Comm., 135, 1015-1021,1986記載の方法により行った。また、α-トコフェロールおよび没食子酸プロピルを対照抗酸化物質として用い、各化合物のマロンジアルデヒド量を50%抑制する被検物質の濃度を算出した(IC50)。その結果を表１に示す。

【００５８】

【表１】検体 IC50(μM)

化合物１（参考化合物）	98
化合物２	83
化合物３	56
化合物４	65

化合物５ 107
化合物１１ 44
トコフェロール 280
没食子酸プロピル 50

＊【００５９】
【発明の効果】抗酸化性を有し医薬品、化粧品、化成品等に有用である新規ベンゾジオキソール誘導体を提供することである。

フロントページの続き

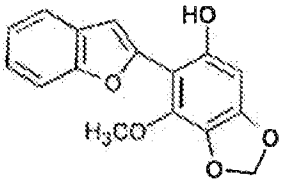
(51)Int.Cl.'	識別記号	FI		テーマコード（参考）
A61K 31/38	601	A61K 31/38	601	
C07D 407/04		C07D 407/04		
409/04		409/04		

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which industry belongs] This invention relates to a new benzo JIOKI sole derivative. It is related with the still more detailed new benzo JIOKI sole derivative which has peroxylipid depressant action with this invention useful to an antioxidant action, medical supplies, etc.
[0002]
[Description of the Prior Art]In recent years, the expectation for an antioxidant is growing as cancer, arteriosclerosis, Parkinson's disease, diabetes mellitus, inflammation, and drugs that the relevance of phenomena, such as aging, and oxidation reaction in the living body is pointed out further, and can control an oxidation mechanism in the living body.
[0003]
[Problem to be solved by the invention]An object of this invention is to provide the benzo JIOKI sole derivative which has peroxylipid depressor effect. Although the compound 1 shown by the following formula (2) is found out as a substance which protects hemolysis of red corpuscles from yeast (J. Am.Chem. Soc., 80, 385-389, 1958), there is no example of a report about the peroxylipid depressor effect of a benzo JIOKI sole derivative.
[0004]
[Chemical formula 2]



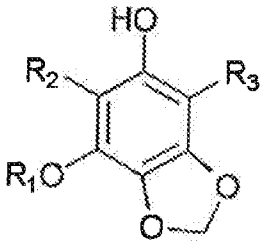
(2)

[0005]

[Means for solving problem]It searches for the character of the compound obtained by this invention's finding out peroxylipid depressor effect to a benzo JIOKI sole derivative, and compounding the intermediate field and these derivatives by organic synthesis, and the new derivative which has a high antioxidant action (peroxylipid depressant action) is provided. This invention is a general formula (1).

[0006]

[Chemical formula 3]



(1)

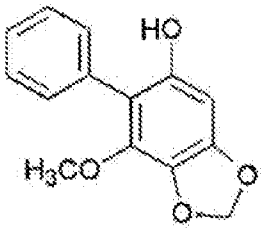
The benzo JIOKI sole derivative expressed with [the arbitrary substituents as which R1 is hydrogen or a low-grade alkyl group, either [at least] R2 or R3 are an aromatic ring or heterocycle (except for a benzofuran ring) here, and the remainder is chosen from hydrogen], and its salt are provided.

[0007]

[Mode for carrying out the invention]This invention is explained in detail below. The "low-grade alkyl group" as used in this invention means the straight chain shape to eight carbon numbers, the shape of a branched chain, or annular. In this invention, "an aromatic ring or heterocycle" means the functional group permitted on Organic Chemistry Division, and they are those substituents objects, such as a phenyl group, a naphthalene group, a thiophene group, a franc group, a pyridine group, and a benzothiophene group. The salt of this invention compound means the salt permitted on medicine manufacture study, and they are sodium salt, potassium salt, calcium salt, ammonium salt, and an aluminum salt. The benzo JIOKI sole derivative of this invention is a new substance, and is useful as a chemical which has peroxylipid depressant action and is used for drugs, cosmetics, a coal chemical product, etc. The manufacturing method is obtained under palladium catalyst existence by using the synthetic method which considers carbon-carbon bonding which used the halogenation benzo JIOKI sole object, the organic boron acid, or the organic tin reagent as a key reaction. An embodiment explains the details of the manufacture.

[0008]It is carried out by check that there is peroxylipid depressant action in a benzo JIOKI sole derivative by this invention, and it is also checked that a new benzo JIOKI sole derivative of this invention has the outstanding peroxylipid depressant action. Therefore, a new benzo JIOKI sole derivative of this invention is useful as a remedy of many diseases considered that a hyperoxidation reaction in the living body is involving, for example, cancer, arteriosclerosis,

Parkinson's disease, diabetes mellitus, and inflammation. A compound of this invention can be made into orally administered drugs, such as various kinds of pharmaceutical forms manufactured according to idiomatic pharmaceutical preparation technology, for example, powder medicine, a granule, a tablet, a glycocalyx agent, ampule, and a capsule, hypodermic, intramuscular or an intravenous administration agent, a suppository, etc. for this purpose. Additive agents, such as the usual extender, a binding material, disintegrator, a pH regulator, and a resolvent, can be used for the above-mentioned pharmaceutical preparation-ization.
[0009]Although a dose to a therapy patient of a new benzo JIOKI sole derivative of this invention may be changed according to a kind, a state, etc. of a patient's age and an illness, it can usually prescribe 10-5000 mg per day for the patient in 1 to several steps to an adult.
[0010]
[Working example]An embodiment explains this invention. An embodiment is one mode of enforcement and does not limit this invention.
[0011](Embodiment 1) Composition of a 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 2) [0012]
[Chemical formula 4]



(3)

[0013]They are acetic acid (13.9 mL) and dichloromethane (5.58.) about a synthetic 4-methoxy-6-hydroxy-1,3-benzo JIOKI sole (2.78 g-16.5 mmol) of a process 1 5-bromo-4-methoxy-6-hydroxy-1,3-benzo JIOKI sole. It dissolved in mL) and agitated at 0 **. A dichloromethane (5.58 mL) solution containing bromine (0.864mL, 16.3 mmol) was dropped there. After 1-hour churning and reaction **** were opened in ice water at a room temperature, and ethyl acetate extracted. Saturated sodium bicarbonate water and a saturation salt solution washed an organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (a developing solvent; hexane : ethyl acetate =4:1) refined residue. It recrystallized with isopropyl ether and the crystal 3.4g (83%) of a mark compound was obtained. The melting point of 77.3 - 78.7 **. 1H NMR (DMSO-d6, 400 MHz) delta 4.07 (3H, s, CH3), 6.0 (2H, m, CH2), 6.46 (1H, s, Ar-H), 8.26 (1H, s, OH).
[0014]Process 2 The 5-bromo-4-methoxy-6-hydroxy-1,3-benzo JIOKI sole (2.55 g, 10.32 mmol) obtained by the synthesizing process 1 of the 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole. It dissolved in dimethylformamide 5 mL and was dropped at the dimethylformamide (2.5 mL) suspension containing sodium hydride (416 mg, 10.4 mmol)

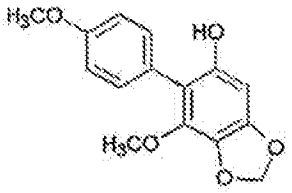
under churning at 0 **. After churning and benzylbromide (1.25 ml, 10.5 mmol) were added for 30 minutes at the room temperature, and it agitated for 30 minutes at the room temperature further. The reaction mixture was opened in ice water and ethyl acetate extracted. Saturated sodium bicarbonate water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =4:1) refines residue, a mark compound is made into an oily matter, and it is 2.78 g. It obtained (80%). 1HNMR (CDCl3,400MHz) delta 4.07 (3H, s, CH3), 5.06 (2H, s, CH2), 5.90 (2H, s, CH2), 6.34 (1H, s, Ar-H), 7.3-7.5 (6H, m, Ar-H).

[0015]Process 3 The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained by the synthesizing process 2 of the 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (300 mg, 0.89 mmol), Phenylboric acid (119 mg, 0.98 mmol), a tetrabutylammonium star's picture (287 mg, 0.89 mmol), Water 2mL was added to palladium acetate (4 mg, 0.018 mmol) and potassium carbonate (307 mg, 2.22 mmol), and it agitated at 90 ** for 1 hour. The reaction mixture was opened in 1N chloride, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =20:1) refined residue. The mark compound was made into the oily matter and obtained 241 mg (81%). 1HNMR (CDCl3,400MHz) delta3.81 (3H, s, CH3), 4.85 (2H, s, CH2), 5.92 (2H, s, CH2), 6.38 (1H, s, Ar-H), 7.1-7.4 (10H, m, Ar-H). MS (EI) m/z 334 (M+, 100%), 243, 213, 91.

[0016]Process 4 The 5-phenyl-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (200 mg) obtained by the synthesizing process 3 of the 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole is dissolved in ethyl acetate (10mL), Pd-C (20 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue, it recrystallized with petroleum ether, and 136 mg (93%) of crystals of the mark compound were obtained. The melting point of 88.1 - 89.4 **. 1HNMR (CDCl3,400MHz) delta3.83 (3H, s, CH3), (1H, brs, OH) 4.78 5.91 (2H, s, CH2), 6.31 (1H, s, Ar-H) 7.32-7.34 (2H, m, Ar-H), 7.37-7.41 (1H, m, Ar-H), and 7.46-7.50 (2H, m, Ar-H). MS(EI) m/z 244 (M+, 100%), 199, 171, 115.

[0017](Embodiment 2) Composition of a 5-(4-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 3) [0018]

[Chemical formula 5]

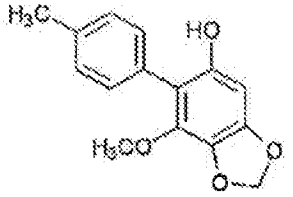


(4)

[0019]The mark compound was obtained like Embodiment 1 except using 4-methoxypheny boric acid instead of the phenylboric acid of Embodiment 1. The melting point of 83.0 - 83.8 **. 1HNMR (CDCl3,400MHz) delta3.83 (3H, s, CH3), 3.85 (3H, s, CH3) 4.79 (1H, brs, OH), 5.90 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.00-7.02 (2H, m, Ar-H), and 7.23-7.25 (2H, m, Ar-H). MS(EI) m/z 274 (M+, 100%), 259, 229, 201, 145.

[0020](Embodiment 3) Composition of a 5-(4-methylphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 4) [0021]

[Chemical formula 6]

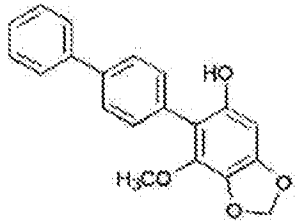


(5)

[0022]The mark compound was obtained like Embodiment 1 except using 4-methylphenyl boric acid instead of the phenylboric acid of Embodiment 1. The melting point of 124.8 - 126.6 **. 1HNMR (CDCl3,400MHz) delta2.40 (3H, s, CH3), 3.83 (3H, s, CH3) 4.80 (1H, brs, OH), 5.90 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.20-7.22 (2H, m, Ar-H), and 7.28-7.30 (2H, m, Ar-H). MS(EI) m/z 258 (M+, 100%), 243, 213, 185, 129.

[0023](Embodiment 4) Composition of a 5-(4-biphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 5) [0024]

[Chemical formula 7]

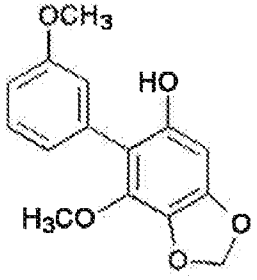


(6)

[0025]The mark compound was obtained like Embodiment 1 except using 4-biphenyl boric acid instead of the phenylboric acid of Embodiment 1. The melting point of 141.8 - 143.5 **. 1HNMR (CDCl3,400MHz) delta3.87 (3H, s, CH3), (1H, brs, OH) 4.86 5.91 (2H, s, CH2), 6.33 (1H, s, Ar-H) 7.35-7.41 (3H, m, Ar-H), 7.44-7.48 (2H, m, Ar-H), 7.63-7.65 (2H, m, Ar-H), 7.68-7.71 (2H, m, Ar-H). MS(EI) m/z 320 (M+, 100%), 275, 247, 191.

[0026](Embodiment 5) Composition of a 5-(3-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 6) [0027]

[Chemical formula 8]

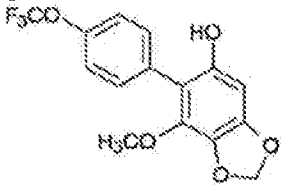


(7)

[0028]A mark compound was obtained like Embodiment 1 except using 3-methoxypheny boric acid instead of phenylboric acid of Embodiment 1. 1HNMR(CDCl3,400MHz) delta 3.83 (3H, s, CH3), (3H, s, CH3) 3.84 4.86 (1H, brs, OH), 5.91 (2H, s, CH2) 6.31 (1H, s, Ar-H), 6.86-6.95 (4H, m, Ar-H), and 7.40 (1H, dd, and J = 7.9, 7.9 Hz Ar-H).

[0029](Embodiment 6) Composition of a 5-(4-trifluoro methylphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 7) [0030]

[Chemical formula 9]

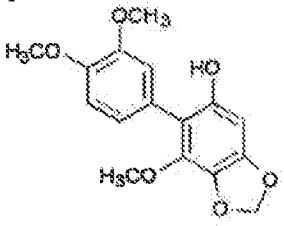


(8)

[0031]A mark compound was obtained like Embodiment 1 except using 4-trifluoromethyl phenylboric acid instead of phenylboric acid of Embodiment 1. 1HNMR(CDCl3,400MHz) delta 3.85 (3H, s, CH3), 4.62 (1H, brs, OH), 5.91 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.30-7.37 (4H, m, Ar-H).

[0032](Embodiment 7) Composition of a 5-(3,4-dimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 8) [0033]

[Chemical formula 10]



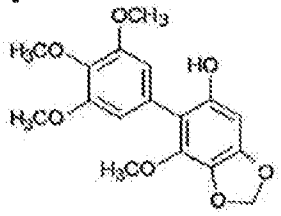
(9)

[0034]A mark compound was obtained like Embodiment 1 except using 3,4-dimethoxyphenylboric acid instead of phenylboric acid of Embodiment 1. 1HNMR (CDCl3,400MHz) delta 3.85 (3H, s, CH3), (3H, s, CH3) 3.88 3.93 (3H, s, CH3), (1H, brs, OH)

4.88 5.90 (2H, s, CH2), 6.31 (1H, s, Ar-H) 6.83 (1H, d, J = 1.9 Hz Ar-H), 6.88 (1H, dd, and J = 1.9, 8.0 Hz Ar-H), 6.98 (1H, d, J = 8.0 Hz Ar-H).

[0035](Embodiment 8) Composition of a 5-(3,4,5-trimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 9) [0036]

[Chemical formula 11]

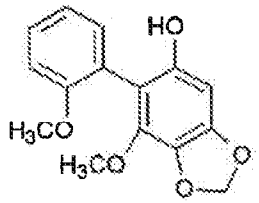


(10)

[0037]The mark compound was obtained like Embodiment 1 except using 3,4,5-trimethoxyphenyl boric acid instead of the phenylboric acid of Embodiment 1. 1HNMR (CDCl3,400MHz) delta3.86 (6H, s, CH3), 3.88 (3H, s, CH3) 3.90 (3H, s, CH3), 4.94 (1H, brs, OH), 5.91 (2H, s, CH2), 6.31 (1H, s, Ar-H), and 6.53 (2H, s, Ar-H).

[0038](Embodiment 9) Composition of a 5-(2-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 10) [0039]

[Chemical formula 12]

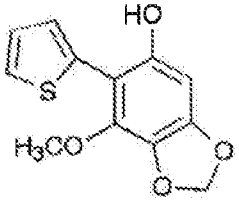


(11)

[0040]The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in Embodiment 1 (360 mg, 1.07 mmol), 2M potassium carbonate solution (0.6 ml) and toluene 6 mL were added to 2-methoxypheny boric acid (240 mg, 1.61 mmol) and tetrakis (triphenyl phosphine) palladium (120 mg, 0.11 mmol), and it agitated at 120 ** for 16 hours. The reaction mixture was opened in 1N chloride, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue. The obtained oily matter was dissolved in ethyl acetate (10 mL), and Pd-C (150 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =3:1) refined residue, and crystal 118 mg (40%) of the mark compound was obtained. 1H NMR(CDCl3,400MHz) delta 3.82 (3H, s, CH3), (3H, s, CH3) 3.83 5.03 (1H, brs, OH), 5.91 (2H, m, CH2) 6.33 (1H, s, Ar-H), 7.03-7.06 (2H, m, Ar-H), 7.22-7.25 (1H, m, Ar-H), and 7.37-7.41 (1H, m, Ar-H).

[0041](Embodiment 10) Composition of a 5-(thienyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 11) [0042]

[Chemical formula 13]



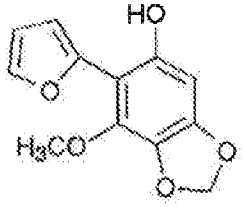
(12)

[0043]Process 1 The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in synthetic Embodiment 1 of the 5-(thienyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (300 mg, 0.89 mmol), 2 -(bird butylstannyl)- HMPA5mL was added to a thiophene (565mL, 1.78 mmol) and tetrakis (triphenyl phosphine) palladium (51 mg, 0.04 mmol), and it agitated at 100 ** for 4 hours. The reaction mixture was opened in 1N chloride, and it extracted with diethylether. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue. 281 mg (93%) was obtained by making a mark compound into an oily matter. 1HNMR (CDCl3,400MHz) delta3.90 (3H, s, CH3), 4.96 (2H, s, CH2) 5.92 (2H, s, CH2), 6.38 (1H, s, Ar-H), 7.06-7.07 (1H, m, Ar-H), 7.27-7.34 (7H, m, Ar-H). MS (EI) m/z 340 (M+), 249 (100%), 219, 91.

[0044]Process 2 The 5-(thienyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (280 mg) obtained by the synthesizing process 1 of the 5-(thienyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole is dissolved in ethyl acetate (10mL), Pd-C (150 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue, it recrystallized with petroleum ether, and 15 mg (7%) of crystals of the mark compound were obtained. The melting point of 75.6 - 77.0 **. 1HNMR (CDCl3,400MHz) delta3.91 (3H, s, CH3), (1H, brs, OH) 5.21 5.91 (2H, s, CH2), (1H, s, Ar-H) 6.31 7.06 (1H, dd, J = 0.8, 3.5 Hz, Ar-H), 7.15 (1H, dd, J = 3.5, 5.0 Hz, Ar-H) 7.48 (1H, dd, J = 0.8, 5.0 Hz, Ar-H). MS (EI) m/z250 (M+, 100%), 235, 219, 205, 121.

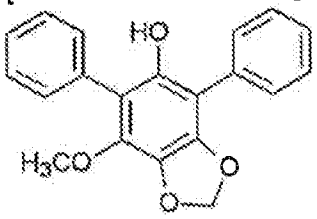
[0045](Embodiment 11) Composition of a 5-(2-franc)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 12) [0046]

[Chemical formula 14]



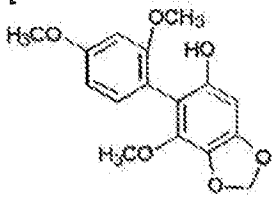
(13)

[0047]The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole of Embodiment 10, 2 -(bird butylstannyl)- Instead of a thiophene, 6-buthyldimethyl **********- 5-bromo-4-methoxy-1,3-benzo JIOKI sole, 2 -(bird butylstannyl)- Except using a franc, the oily matter produced by making it be the same as that of Embodiment 10 was dissolved in THF, deprotection of the TBAF was added and carried out, and the mark compound was obtained. 1HNMR (CDCl3,400MHz) delta 4.00 (3H, s, CH3), (1H, brs, OH) 7.4 5.90 (2H, s, CH2), 6.29 (1H, s, Ar-H) 6.53-6.54 (1H, m, Ar-H), 6.73-6.74 (1H, m, Ar-H), and 7.48-7.49 (1H, m, Ar-H).
[0048](Embodiment 12) Composition of a 1,5-diphenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 13) [0049]
[Chemical formula 15]



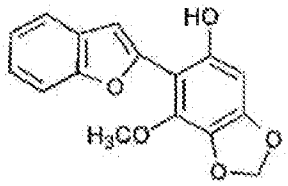
(14)

The mark compound was obtained like Embodiment 1 except using a 6-benzyloxy 1,5-dibromo-4-methoxy-1,3-benzo JIOKI sole instead of the 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole of Embodiment 1. 1HNMR (CDCl3,400MHz) delta3.86 (3H, s, CH3), 4.93 (1H, brs, OH), 5.93 (2H, s, CH2), and 7.37-7.59 (10H, m, Ar-H).
[0050](Embodiment 13) Composition of a 5-(2,4-dimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 14) [0051]
[Chemical formula 16]



(15)

[0052]The mark compound was obtained like Embodiment 9 except using 2,4-dimethoxyphenylboric acid instead of 2-methoxypheny boric acid of Embodiment 9. 1HNMR (CDCl3,400MHz) delta 3.80 (3H, s, CH3), (3H, s, CH3) 3.81 3.85 (3H, s, CH3), 4.96 (1H, brs, OH) 5.90 (2H, m, CH2), 6.32 (1H, s, Ar-H), 6.60-6.62 (2H, m, Ar-H), 7.12-7.14 (1H, m, Ar-H).
[0053](Reference example) Composition of a 5-(2-benzofuranyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 1)
[0054]
[Chemical formula 17]



(2)

[0055]The process 1 A 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in synthetic Embodiment 1 of a 5-(2-benzofuranyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (960 mg, 2.82 mmol), Benzofuran-2-boric acid (684 mg, 4.22 mmol), tris(o-toluyl) phosphine (128 mg, 0.421 mmol), A trisbenzylideneacetone 2 palladium chloroform complex (109 mg, 0.105 mmol) and diisopropylethylamine (0.982 g-5.64 mmol) were dissolved in dimethylformamide 10mL, and it agitated at 90 ** for 1 hour. A reaction mixture was opened in ice water and ethyl acetate extracted. Water and a saturation salt solution washed an organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (a developing solvent; hexane : benzene =1:1) refined residue. A mark compound was made into an oily matter and obtained 1.14g (100%). 1HNMR (CDCl3,400MHz) delta3.95 (3H, s, CH3), 5.01 (2H, s, CH2) 5.95 (2H, s, CH2), 6.39 (1H, s, Ar-H), 6.83 (1H, s, Ar-H), 6.8-7.6 (10H, m, Ar-H). MS(EI) m/z 374, 283, 255.

[0056]Process 2 The 5-(2-benzofuranyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole obtained by the synthesizing process 1 of the 5-(2-benzofuranyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (1.14 g-3.04 mmol), It dissolved in ethyl acetate (70mL), and Pd-C (56 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; ethyl acetate : hexane =15:85) refined residue. It recrystallized with petroleum ether and 715 mg (88%) of mark compounds were obtained. The melting point of 118 **. 1HNMR (Acetone-d6, 400 MHz) delta3.95 (3H, s, CH3), 5.06 (2H, s, CH2) 5.98 (2H, s, CH2), 6.31 (1H, s, Ar-H), 6.93 (1H, s, Ar-H), 7.2-7.6 (6H, m, Ar-H), and 8.33 (1H, s, OH). MS(EI) m/z 284, 269, 142.

[0057](Antioxidation activity measurement test) The peroxylipid inhibition test was done by the method of Biochem.Biophys.Res. Comm., 135, and 1015 -1021-1986 description. The concentration of the specimen material which controls the amount of malondialdehydes of each compound 50% was computed, using the alpha-tocopherol and propyl gallate as a contrast antioxidant (IC_{50}). The result is shown in Table 1.

[0058]

[Table 1]Sample IC50 (muM) compound 1 (reference compound) 98 compound 2 83 compounds 3 56 compounds 4 65 compounds 5 107 compounds 11 44 tocopherol 280 propyl-gallate 50[0059]

[Effect of the Invention]It is having antioxidation nature and providing drugs, cosmetics, a coal

chemical product, etc. with a useful new benzo JIOKI sole derivative.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

PRIOR ART

[Description of the Prior Art]In recent years, the expectation for an antioxidant is growing as cancer, arteriosclerosis, Parkinson's disease, diabetes mellitus, inflammation, and drugs that the relevance of phenomena, such as aging, and oxidation reaction in the living body is pointed out further, and can control an oxidation mechanism in the living body.

[Translation done.]

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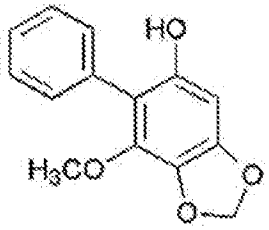
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

EXAMPLE

[Working example]An embodiment explains this invention. An embodiment is one mode of enforcement and does not limit this invention.
[0011](Embodiment 1) Composition of a 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 2) [0012]
[Chemical formula 4]



(3)

[0013]They are acetic acid (13.9 mL) and dichloromethane (5.58.) about the synthetic 4-methoxy-6-hydroxy-1,3-benzo JIOKI sole (2.78 g-16.5 mmol) of a process 1 5-bromo-4-methoxy-6-hydroxy-1,3-benzo JIOKI sole. It dissolved in mL) and agitated at 0 **. The dichloromethane (5.58 mL) solution containing bromine (0.864mL, 16.3 mmol) was dropped there. After 1-hour churning and reaction **** were opened in ice water at the room temperature, and ethyl acetate extracted. Saturated sodium bicarbonate water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =4:1) refined residue. It recrystallized with isopropyl ether and the crystal 3.4g (83%) of the mark compound was obtained. The melting point of 77.3 - 78.7 **. 1H NMR (DMSO-d6, 400 MHz) delta 4.07 (3H, s, CH3), 6.0 (2H, m, CH2), 6.46 (1H, s, Ar-H), 8.26 (1H, s, OH).
[0014]Process 2 The 5-bromo-4-methoxy-6-hydroxy-1,3-benzo JIOKI sole (2.55 g, 10.32 mmol) obtained by the synthesizing process 1 of the 6-benzyloxy 5-bromo-4-methoxy-1,3-

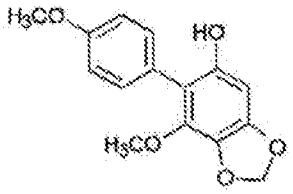
benzo JIOKI sole. It dissolved in dimethylformamide 5 mL and was dropped at the dimethylformamide (2.5 mL) suspension containing sodium hydride (416 mg, 10.4 mmol) under churning at 0 **. After churning and benzylbromide (1.25 ml, 10.5 mmol) were added for 30 minutes at the room temperature, and it agitated for 30 minutes at the room temperature further. The reaction mixture was opened in ice water and ethyl acetate extracted. Saturated sodium bicarbonate water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =4:1) refines residue, a mark compound is made into an oily matter, and it is 2.78 g. It obtained (80%). 1HNMR (CDCl3,400MHz) delta 4.07 (3H, s, CH3), 5.06 (2H, s, CH2), 5.90 (2H, s, CH2), 6.34 (1H, s, Ar-H), 7.3-7.5 (6H, m, Ar-H).

[0015]Process 3 The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained by the synthesizing process 2 of the 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (300 mg, 0.89 mmol), Phenylboric acid (119 mg, 0.98 mmol), a tetrabutylammonium star's picture (287 mg, 0.89 mmol), Water 2mL was added to palladium acetate (4 mg, 0.018 mmol) and potassium carbonate (307 mg, 2.22 mmol), and it agitated at 90 ** for 1 hour. The reaction mixture was opened in 1N chloride, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =20:1) refined residue. The mark compound was made into the oily matter and obtained 241 mg (81%). 1HNMR (CDCl3,400MHz) delta3.81 (3H, s, CH3), 4.85 (2H, s, CH2), 5.92 (2H, s, CH2), 6.38 (1H, s, Ar-H), 7.1-7.4 (10H, m, Ar-H). MS (EI) m/z 334 (M+, 100%), 243, 213, 91.

[0016]The process 4 A 5-phenyl-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (200 mg) obtained by the synthesizing process 3 of a 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole is dissolved in ethyl acetate (10mL), Pd-C (20 mg) was added 10%, and at a room temperature, it agitated overnight and hydrogenated. A reaction mixture was filtered and condensed. Silica gel column chromatography (a developing solvent; hexane : ethyl acetate =5:1) refined residue, it recrystallized with petroleum ether, and 136 mg (93%) of crystals of a mark compound were obtained. The melting point of 88.1 - 89.4 **. 1HNMR (CDCl3,400MHz) delta3.83 (3H, s, CH3), (1H, brs, OH) 4.78 5.91 (2H, s, CH2), 6.31 (1H, s, Ar-H) 7.32-7.34 (2H, m, Ar-H), 7.37-7.41 (1H, m, Ar-H), and 7.46-7.50 (2H, m, Ar-H). MS(EI) m/z 244 (M+, 100%), 199, 171, 115.

[0017](Embodiment 2) Composition of a 5-(4-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 3) [0018]

[Chemical formula 5]

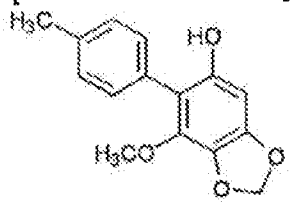


(4)

[0019]A mark compound was obtained like Embodiment 1 except using 4-methoxypheny boric acid instead of phenylboric acid of Embodiment 1. The melting point of 83.0 - 83.8 **. 1HNMR (CDCl3,400MHz) delta3.83 (3H, s, CH3), 3.85 (3H, s, CH3) 4.79 (1H, brs, OH), 5.90 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.00-7.02 (2H, m, Ar-H), and 7.23-7.25 (2H, m, Ar-H). MS(EI) m/z 274 (M+, 100%), 259, 229, 201, 145.

[0020](Embodiment 3) Composition of a 5-(4-methylphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 4) [0021]

[Chemical formula 6]

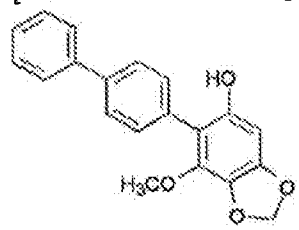


(5)

[0022]A mark compound was obtained like Embodiment 1 except using 4-methylphenyl boric acid instead of phenylboric acid of Embodiment 1. The melting point of 124.8 - 126.6 **. 1HNMR (CDCl3,400MHz) delta2.40 (3H, s, CH3), 3.83 (3H, s, CH3) 4.80 (1H, brs, OH), 5.90 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.20-7.22 (2H, m, Ar-H), and 7.28-7.30 (2H, m, Ar-H). MS(EI) m/z 258 (M+, 100%), 243, 213, 185, 129.

[0023](Embodiment 4) Composition of a 5-(4-biphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 5) [0024]

[Chemical formula 7]

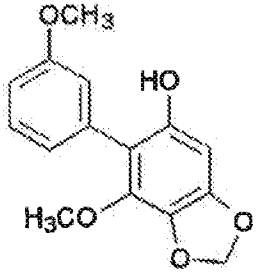


(6)

[0025]A mark compound was obtained like Embodiment 1 except using 4-biphenyl boric acid instead of phenylboric acid of Embodiment 1. The melting point of 141.8 - 143.5 **. 1HNMR (CDCl3,400MHz) delta3.87 (3H, s, CH3), (1H, brs, OH) 4.86 5.91 (2H, s, CH2), 6.33 (1H, s, Ar-H) 7.35-7.41 (3H, m, Ar-H), 7.44-7.48 (2H, m, Ar-H), 7.63-7.65 (2H, m, Ar-H), 7.68-7.71 (2H, m, Ar-H). MS(EI) m/z 320 (M+, 100%), 275, 247, 191.

[0026](Embodiment 5) Composition of a 5-(3-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 6) [0027]

[Chemical formula 8]

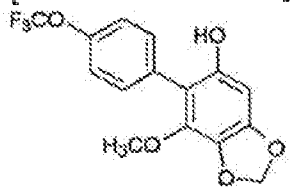


(7)

[0028]The mark compound was obtained like Embodiment 1 except using 3-methoxypheny boric acid instead of the phenylboric acid of Embodiment 1. 1HNMR(CDCl3,400MHz) delta 3.83 (3H, s, CH3), (3H, s, CH3) 3.84 4.86 (1H, brs, OH), 5.91 (2H, s, CH2) 6.31 (1H, s, Ar-H), 6.86-6.95 (4H, m, Ar-H), and 7.40 (1H, dd, and J = 7.9, 7.9 Hz Ar-H).

[0029](Embodiment 6) Composition of a 5-(4-trifluoro methylphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 7) [0030]

[Chemical formula 9]

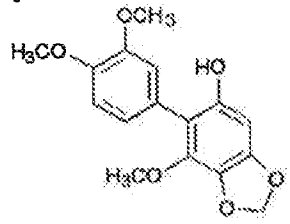


(8)

[0031]The mark compound was obtained like Embodiment 1 except using 4-trifluoromethyl phenylboric acid instead of the phenylboric acid of Embodiment 1. 1HNMR(CDCl3,400MHz) delta 3.85 (3H, s, CH3), 4.62 (1H, brs, OH), 5.91 (2H, s, CH2), 6.30 (1H, s, Ar-H), 7.30-7.37 (4H, m, Ar-H).

[0032](Embodiment 7) Composition of a 5-(3,4-dimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 8) [0033]

[Chemical formula 10]



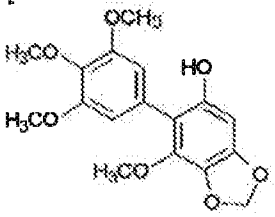
(9)

[0034]The mark compound was obtained like Embodiment 1 except using 3,4-dimethoxyphenylboric acid instead of the phenylboric acid of Embodiment 1. 1HNMR (CDCl3,400MHz) delta 3.85 (3H, s, CH3), (3H, s, CH3) 3.88 3.93 (3H, s, CH3), (1H, brs, OH)

4.88 5.90 (2H, s, CH2), 6.31 (1H, s, Ar-H) 6.83 (1H, d, J = 1.9 Hz Ar-H), 6.88 (1H, dd, and J = 1.9, 8.0 Hz Ar-H), 6.98 (1H, d, J = 8.0 Hz Ar-H).

[0035](Embodiment 8) Composition of a 5-(3,4,5-trimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 9) [0036]

[Chemical formula 11]

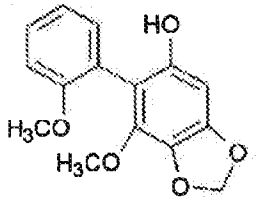


(10)

[0037]The mark compound was obtained like Embodiment 1 except using 3,4,5-trimethoxyphenyl boric acid instead of the phenylboric acid of Embodiment 1. 1HNMR (CDCl3,400MHz) delta3.86 (6H, s, CH3), 3.88 (3H, s, CH3) 3.90 (3H, s, CH3), 4.94 (1H, brs, OH), 5.91 (2H, s, CH2), 6.31 (1H, s, Ar-H), and 6.53 (2H, s, Ar-H).

[0038](Embodiment 9) Composition of a 5-(2-methoxypheny)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 10) [0039]

[Chemical formula 12]

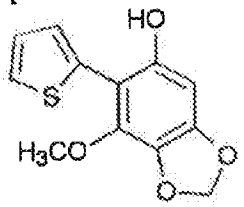


(11)

[0040]The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in Embodiment 1 (360 mg, 1.07 mmol), 2M potassium carbonate solution (0.6 ml) and toluene 6 mL were added to 2-methoxypheny boric acid (240 mg, 1.61 mmol) and tetrakis (triphenyl phosphine) palladium (120 mg, 0.11 mmol), and it agitated at 120 ** for 16 hours. The reaction mixture was opened in 1N chloride, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue. The obtained oily matter was dissolved in ethyl acetate (10 mL), and Pd-C (150 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =3:1) refined residue, and crystal 118 mg (40%) of the mark compound was obtained. 1H NMR(CDCl3,400MHz) delta 3.82 (3H, s, CH3), (3H, s, CH3) 3.83 5.03 (1H, brs, OH), 5.91 (2H, m, CH2) 6.33 (1H, s, Ar-H), 7.03-7.06 (2H, m, Ar-H), 7.22-7.25 (1H, m, Ar-H), and 7.37-7.41 (1H, m, Ar-H).

[0041](Embodiment 10) Composition of a 5-(thienyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 11) [0042]

[Chemical formula 13]



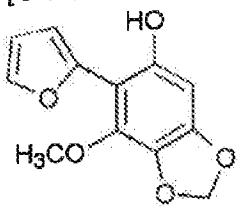
(12)

[0043]Process 1 The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in synthetic Embodiment 1 of the 5-(thienyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (300 mg, 0.89 mmol), 2 -(bird butylstannyl)- HMPA5mL was added to a thiophene (565mL, 1.78 mmol) and tetrakis (triphenyl phosphine) palladium (51 mg, 0.04 mmol), and it agitated at 100 ** for 4 hours. The reaction mixture was opened in 1N chloride, and it extracted with diethylether. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue. 281 mg (93%) was obtained by making a mark compound into an oily matter. 1HNMR (CDCl3,400MHz) delta3.90 (3H, s, CH3), 4.96 (2H, s, CH2) 5.92 (2H, s, CH2), 6.38 (1H, s, Ar-H), 7.06-7.07 (1H, m, Ar-H), 7.27-7.34 (7H, m, Ar-H). MS (EI) m/z 340 (M+), 249 (100%), 219, 91.

[0044]Process 2 The 5-(thienyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (280 mg) obtained by the synthesizing process 1 of the 5-(thienyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole is dissolved in ethyl acetate (10mL), Pd-C (150 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; hexane : ethyl acetate =5:1) refined residue, it recrystallized with petroleum ether, and 15 mg (7%) of crystals of the mark compound were obtained. The melting point of 75.6 - 77.0 **. 1HNMR (CDCl3,400MHz) delta3.91 (3H, s, CH3), (1H, brs, OH) 5.21 5.91 (2H, s, CH2), (1H, s, Ar-H) 6.31 7.06 (1H, dd, J = 0.8, 3.5 Hz, Ar-H), 7.15 (1H, dd, J = 3.5, 5.0 Hz, Ar-H) 7.48 (1H, dd, J = 0.8, 5.0 Hz, Ar-H). MS (EI) m/z250 (M+, 100%), 235, 219, 205, 121.

[0045](Embodiment 11) Composition of a 5-(2-franc)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 12) [0046]

[Chemical formula 14]

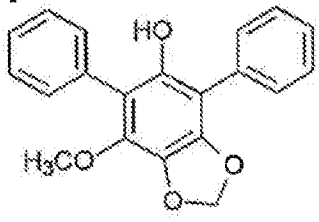


(13)

[0047]The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole of Embodiment 10, 2 -(bird butylstannyl)- Instead of a thiophene, 6-buthyldimethyl **********- 5-bromo-4-methoxy-1,3-benzo JIOKI sole, 2 -(bird butylstannyl)- Except using a franc, the oily matter produced by making it be the same as that of Embodiment 10 was dissolved in THF, deprotection of the TBAF was added and carried out, and the mark compound was obtained. 1HNMR (CDCl3,400MHz) delta 4.00 (3H, s, CH3), (1H, brs, OH) 7.4 5.90 (2H, s, CH2), 6.29 (1H, s, Ar-H) 6.53-6.54 (1H, m, Ar-H), 6.73-6.74 (1H, m, Ar-H), and 7.48-7.49 (1H, m, Ar-H).

[0048](Embodiment 12) Composition of a 1,5-diphenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 13) [0049]

[Chemical formula 15]

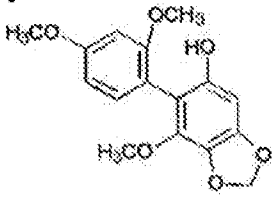


(14)

The mark compound was obtained like Embodiment 1 except using a 6-benzyloxy 1,5-dibromo-4-methoxy-1,3-benzo JIOKI sole instead of the 5-phenyl-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole of Embodiment 1. 1HNMR (CDCl3,400MHz) delta3.86 (3H, s, CH3), 4.93 (1H, brs, OH), 5.93 (2H, s, CH2), and 7.37-7.59 (10H, m, Ar-H).

[0050](Embodiment 13) Composition of a 5-(2,4-dimethoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (compound 14) [0051]

[Chemical formula 16]



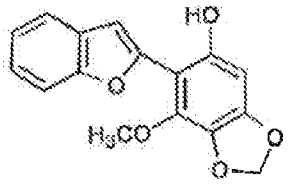
(15)

[0052]The mark compound was obtained like Embodiment 9 except using 2,4-dimethoxyphenylboric acid instead of 2-methoxypheny boric acid of Embodiment 9. 1HNMR (CDCl3,400MHz) delta 3.80 (3H, s, CH3), (3H, s, CH3) 3.81 3.85 (3H, s, CH3), 4.96 (1H, brs, OH) 5.90 (2H, m, CH2), 6.32 (1H, s, Ar-H), 6.60-6.62 (2H, m, Ar-H), 7.12-7.14 (1H, m, Ar-H).

[0053](Reference example) composition (compound 1) of a 5-(2-benzofuranyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole

[0054]

[Chemical formula 17]



(2)

[0055]Process 1 The 6-benzyloxy 5-bromo-4-methoxy-1,3-benzo JIOKI sole obtained in synthetic Embodiment 1 of the 5-(2-benzofuranyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole (960 mg, 2.82 mmol), Benzofuran-2-boric acid (684 mg, 4.22 mmol), tris(o-toluyl) phosphine (128 mg, 0.421 mmol), A trisbenzylideneacetone 2 palladium chloroform complex (109 mg, 0.105 mmol) and diisopropylethylamine (0.982 g-5.64 mmol) were dissolved in dimethylformamide 10mL, and it agitated at 90 ** for 1 hour. The reaction mixture was opened in ice water and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer one by one, and it dried and condensed with anhydrous magnesium sulfate. Silica gel column chromatography (developing solvent; hexane : benzene =1:1) refined residue. The mark compound was made into the oily matter and obtained 1.14g (100%). 1HNMR (CDCl3,400MHz) delta3.95 (3H, s, CH3), 5.01 (2H, s, CH2) 5.95 (2H, s, CH2), 6.39 (1H, s, Ar-H), 6.83 (1H, s, Ar-H), 6.8-7.6 (10H, m, Ar-H). MS(EI) m/z 374, 283, 255.

[0056]Process 2 The 5-(2-benzofuranyl)-6-benzyloxy 4-methoxy-1,3-benzo JIOKI sole obtained by the synthesizing process 1 of the 5-(2-benzofuranyl)-6-hydroxy-4-methoxy-1,3-benzo JIOKI sole (1.14 g-3.04 mmol), It dissolved in ethyl acetate (70mL), and Pd-C (56 mg) was added 10%, and at the room temperature, it agitated overnight and hydrogenated. The reaction mixture was filtered and condensed. Silica gel column chromatography (developing solvent; ethyl acetate : hexane =15:85) refined residue. It recrystallized with petroleum ether and 715 mg (88%) of mark compounds were obtained. The melting point of 118 **. 1HNMR (Acetone-d6, 400 MHz) delta3.95 (3H, s, CH3), 5.06 (2H, s, CH2) 5.98 (2H, s, CH2), 6.31 (1H, s, Ar-H), 6.93 (1H, s, Ar-H), 7.2-7.6 (6H, m, Ar-H), and 8.33 (1H, s, OH). MS(EI) m/z 284, 269, 142.

[0057](Antioxidation activity measurement test) The peroxylipid inhibition test was done by the method of Biochem.Biophys.Res. Comm., 135, and 1015 -1021-1986 description. The concentration of the specimen material which controls the amount of malondialdehydes of each compound 50% was computed, using the alpha-tocopherol and propyl gallate as a contrast antioxidant (IC_{50}). The result is shown in Table 1.

[0058]

[Table 1]The sample IC50 (muM) compound 1 (reference compound) 98 compound 2 The 83 compounds 3 The 56 compounds 4 The 65 compounds 5 The 107 compounds 11 44 tocopherol 280 propyl-gallate 50

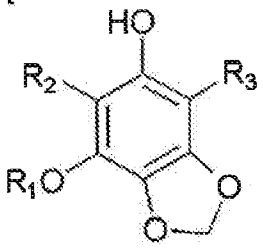
[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]A general formula (1)
[Chemical formula 1]



(1)

[Here, R1 is hydrogen or a low-grade alkyl group, and either [at least] R2 or R3 are an aromatic ring or heterocycle (except for a benzofuran ring).
A benzo JIOKI sole derivative by which the remainder is expressed with arbitrary substituents chosen from hydrogen], and its salt.

[Claim 2]A benzo JIOKI sole derivative of Claim 1 whose R2 is an aromatic ring or heterocycle (except for a benzofuran ring) at least among a general formula (1).

[Translation done.]